

CASE REPORT

Parvovirus B19 infection associated with hemolytic anemia and cranial polyneuropathy

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Received: 15 May 2017 / Revised: 29 June 2017 / Accepted: 26 July 2017
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Abstract Parvovirus B19 (PB19) is a common, widespread, small, single-stranded DNA virus which has been linked with a broad spectrum of clinical illnesses, including a variety of neurological complications such as encephalitis, meningitis, myelitis, stroke, cerebellar ataxia, and neuropathy. The authors describe a case of PB19 infection associated with hemolytic anemia and cranial polyneuropathy involving the second and third cranial nerves in a 23-year-old immunocompetent woman. The diagnosis of acute PB19 infection was established with detection of positive DNA and anti-PB19 IgM antibodies in blood samples. Antiganglioside antibody studies were performed and serum anti-GD1b IgG was strongly positive. Further investigation was normal or negative, excluding other infectious or autoimmune disorders. The patient was initially treated with a 5-day course of intravenous immunoglobulin (IGIV). Because of incomplete neurological recovery, methylprednisolone was also administered 7 days after IGIV therapy initiation. Complete resolution of clinical symptoms was observed 3 months after disease onset at follow-up visit, despite the persistence of PB19 DNA and anti-PB19 IgM antibodies in serum 5 months after the initial presentation. Our report provides evidence that PB19 could affect both the central and peripheral nervous system, possibly by triggering an autoimmune mechanism that leads to autoantibody production.

Keywords Parvovirus B19 · Infection · Autoantibodies · Hemolytic anemia · Cranial neuropathy

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Introduction

Parvovirus B19 (PB19) is a common, widespread, small, single-stranded DNA virus which has been linked with a broad spectrum of clinical illnesses, ranging from self-limiting erythema infectiosum in the healthy host to life-threatening complications in immunocompromised patients (Qiu et al. 2017; Broliden et al. 2006). In rare cases, PB19 infection could be related with less commonly recognized and infrequently reported neurological manifestations. We describe a case of PB19 infection associated with cranial polyneuropathy and hemolytic anemia in a 23-year-old immunocompetent woman.

Case report

A previously healthy 23-year-old woman presented to our emergency department with a 2-day history of acute right eye pain during eye movement followed by ipsilateral blurring vision, pupillary asymmetry, and double vision 2 weeks after a spontaneously resolved diarrheal episode. Neurological examination showed an uncorrected visual acuity of 7/10 in her right eye and a relative afferent pupillary defect, anisocoria with an ipsilateral dilated pupil, paresis of right eye adduction, and vertical diplopia in all directions of gaze. The remaining clinical examination was otherwise normal. Cerebral computed tomography, brain magnetic resonance imaging (Fig. 1), and magnetic resonance angiography were normal. Initial laboratory testing revealed a mild increase of total bilirubin (1.85 mg/dL; normal range < 1.20 mg/dL) and direct bilirubin (0.52 mg/dL; normal range < 0.50 mg/dL) levels, whereas other liver and renal function tests, hemoglobin, white blood cell count, erythrocyte sedimentation rate, and C-reactive protein were normal. Autoimmune screening was negative for antinuclear antibodies,

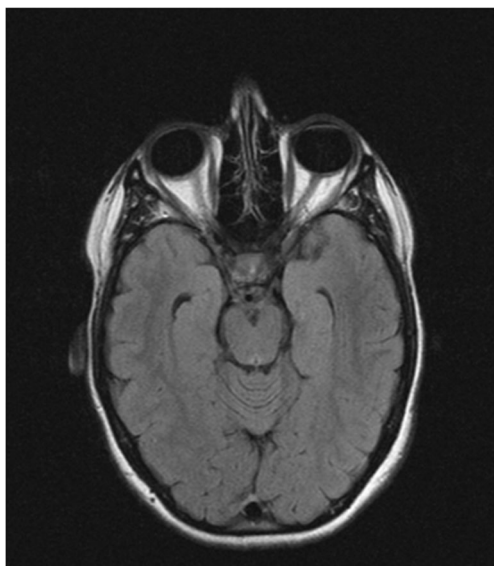


Fig. 1 Normal brain magnetic resonance imaging (axial T2 FLAIR)

antineutrophil cytoplasmic antibodies, antithyroid antibodies, and serum angiotensin converting enzyme. Antiganglioside antibody studies were performed and serum anti-GD1b IgG was strongly positive. Cerebrospinal fluid (CSF) exhibited normal cell count and protein level, absence of IgG bands or intrathecal IgG synthesis, and the presence of a damaged blood-brain barrier. Serological tests in serum and CSF excluded active infection due to enterovirus, herpes simplex virus 1 and 2, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus 1 and 2, *Treponema pallidum*, and *Borrelia burgdorferi*. Additional blood investigations displayed positive anti-PB19 IgM (3.20; positive ≥ 1.0) and IgG (40.90; positive ≥ 1.0) antibodies, and PB19 DNA was detected using polymerase chain reaction

(PCR). Search for PB19 DNA in CSF with PCR was negative. A diagnosis of PB19-associated cranial polyneuropathy involving the second and third cranial nerves was made and the patient was initially treated with a 5-day course of intravenous immunoglobulin (IVIG) 30 g/day. Because of incomplete neurological recovery, methylprednisolone 1 g daily for 5 days was also administered 7 days after IGIV therapy initiation. During her stay in the hospital, she developed an episode of self-limited hemolytic anemia with a low hemoglobin count (9.7 g/dL; normal range > 12.0 g/dL) and increased total bilirubin (5.72 mg/dL) and direct bilirubin (0.66 mg/dL) levels. Progressive neurological improvement was observed and the patient was discharged 21 days after admittance, maintaining anisocoria and paresis of right eye adduction. Complete resolution of clinical symptoms was observed 3 months after admission at follow-up visit. Repeated laboratory workup in serum 5 months after the initial presentation evidenced the persistence of PB19 DNA and anti-PB19 IgM (1.10; positive ≥ 1.0) and IgG (32.50; positive ≥ 1.0) antibodies but was negative regarding antiganglioside antibody studies.

Discussion

A variety of neurological complications have been associated with PB19 infection, including encephalitis, meningitis, myelitis, stroke, cerebellar ataxia, and neuropathy (Barah et al. 2003; Barah et al. 2014; Douvoyiannis et al. 2009), thus demonstrating the ability of virus to involve either the central or peripheral nervous system. The present report illustrates a case of PB19 infection characterized by cranial polyneuropathy and hemolytic

Table 1 Causes of multiple cranial neuropathies involving the second and third cranial nerves

Infectious	Inflammatory	Vascular	Neoplastic	Other
Viruses:	Sarcoidosis	Carotid cavernous fistula	Head and neck tumors	Iatrogenic
Epstein-Barr virus	Systemic lupus erythematosus	Carotid cavernous aneurysm	Neural tumors	Traumatic
Human immunodeficiency virus	Churg-Strauss syndrome	Cavernous sinus thrombosis	Hematologic malignancies	
Varicella zoster virus	Wegener granulomatosis	Sickle cell anemia	Metastatic lesions	
Cytomegalovirus	Giant cell arteritis		Leptomeningeal carcinomatosis	
Bacteria:	Tolosa-Hunt syndrome			
Borrelia burgdorferi				
Treponema pallidum				
Mycobacterium tuberculosis				
Fungi:				
Aspergillosis				
Mucormycosis				
Parasites:				
Toxoplasma gondii				

anemia in an immunologically healthy woman. Interestingly, no other typical PB19-related symptoms such as rash or arthropathy were observed. Visual loss and ophthalmoplegia are often caused by infectious, inflammatory, neoplastic, and vascular processes (Table 1) (Keane 2005). Detailed microbiological and virological tests ruled out a variety of acute infections, but showed elevated titers of PB19 IgM and IgG. Other inflammatory, neoplastic, or vascular disorders were also excluded based on normal imaging and autoimmune studies. The diagnosis of acute PB19 infection was established with detection of positive DNA and anti-PB19 IgM antibodies in blood samples. As PB19 DNA may be detectable for extended periods of time in serum (Musiani et al. 1995), its detection does not indicate acute infection. However, in our case, the presence of immunoglobulin M during the acute neurological deficit, together with the simultaneous development of self-limited hemolytic anemia, suggests a pathogenic role of PB19. Although not completely understood, the pathogenesis of PB19 is complex and several mechanisms may be involved during a single infection, including direct effects of the viral particle, dysregulated immune response with cytokine up-regulation, immune complex deposition, and cytotoxic properties of NS1 protein (Barah et al. 2003). In addition, PB19 infection has been shown to be a trigger for development of a vast array of autoimmune conditions and autoantibody production (Kerr 2016). In our case, the transient detection of antiganglioside GD1b antibodies might represent the pathogenic mechanism by which PB19 affected the central and peripheral nervous system. Antiganglioside antibodies were previously described in PB19-associated Guillain-Barré syndrome (Yamaoka et al. 2000) but not in PB19-related central nervous system manifestations. In our view, PB19 infection induced serum antibody production against GD1b by means of an eventual molecular mimicry mechanism (Kerr 2016). The concept of PB19-induced immune dysfunction led to treatment of its neurological complications with corticosteroids and IGIV, though numerous

patients improve spontaneously (Qiu et al. 2017). Our patient was primarily treated with IVIG and later with methylprednisolone due to incomplete recovery. Fortunately, subsequent resolution of symptoms was observed 3 months after disease onset despite the persistence of PB19 DNA and anti-PB19 IgM antibodies 5 months after the initial presentation. In conclusion, our report provides evidence that PB19 could affect both the central and peripheral nervous system, possibly by triggering an autoimmune mechanism that leads to autoantibody production. Furthermore, our case also suggests that investigation of PB19 infection should be considered even in the absence of typical associated features and regardless of immune status.

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